

Atty. Dkt. No. 041673-2054

2001)(neurotrophins expressed at one site in the brain exert trophic influence over growth among neuronal populations in proximal tissues; copy enclosed for ease of reference).

Dependent claims have also been added to be drawn to a preferred embodiment of the invention, wherein (based on the primate brain as a model) the vectors are directly introduced into the brain at particular distances from targeted cells, as well as at specific intervals from one another, to intensify exposure of target cells to expressed neurotrophin. Support for these claims is found in the limitations of original Claim 1, as well as elsewhere in the specification at page 2, lines 22-26.

Dependent claims have further been added to be drawn to methods for use of particular expression vectors and delivery of particular neurotrophins. Support for the limitations drawn to the vectors is found in the Specification at page 9, lines 14-20 (vectors known to reproduce in non-dividing cells), while support for the limitations drawn to the neurotrophins is found in the Specification at page 7, line 20 through page 8, line 24, and in the Examples.

B. Obviousness-type Double Patenting Rejection.

Applicant will submit a terminal disclaimer as required on patenting of the claims of the '174 Application cited.

C. Response to Claim Rejections under Section 112, Second Paragraph

Claim 7 is rejected for lack of antecedent basis for the term "transgene" therein. The claim has been amended to correct the deficiency.

D. Response to Objections to the Specification and Requirement for Updated Statement Re Priority Claim

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Correction of the deficiencies noted (abstract in excess of 150 words; claiming convention for page 30; and, identification of relationship of the '174 application to the '543 application) has been made by the foregoing amendments.

E. Response to Rejection of Claims 1-12 under Section 112, First Paragraph

The present enablement rejection was also raised in the parent application, Serial No. 09/620,174, on the substantially the same grounds stated in the current Office Action. The rejection was overcome in the parent application on the basis of evidence supplied in that application and in the Examples of the present application with respect to the ability of the art to practice gene therapy (Office Action beginning at page 7). Applicants submit that the same evidence compels reconsideration and withdrawal of the rejection of the present claims under 35 U.S.C. § 112, first paragraph.

In particular, Applicants submit that reconsideration of the application and art will reveal that the specification meets all of the criteria for enablement of the claims set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988): (1) the quantity of experimentation necessary, (2) the amount of discretion or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Of the *Wands* factors, the Office Action focuses on the seventh, contending that "the state of the art for gene therapy in vivo was unpredictable at the time of the invention." (Office Action at page 7). Unpredictability is asserted to lie in the question of whether expression achievable in the invention can provide "therapeutic effects to ameliorate the defective, diseased or damaged cholinergic neurons *in vivo*," (Office Action at page 9) and whether neurotrophins other than GDNF, whose use is exemplified in the application, may be reasonably expected to function in the invention (Office Action, pages 9-10).

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As to transfection, the Action suggests that direct injection of neurotrophin-encoding vectors into brain tissue is limited by the skull, and by the presence of non-dividing cells in the brain. (Office Action at page 8, citing Castro, *et al.*). Applicant disagrees with this conclusion. Clearly, direct injection of vectors into the brain is not only possible in a surgical environment, but is being practiced in current clinical trials. Applicant is further unaware of any evidence to suggest that alternative means of administration (e.g., infusion) would not work in the invention, with proper control of side effects. Indeed, the art is to the contrary (see, e.g., Hermens and Verhaagen, *Prog. Neurobiol.*, 55:399-432 (1998)(infusion of viral vectors into the central nervous system produces desired physiological responses, notwithstanding immune responses to infusion; abstract enclosed, full article will be provided on request). However, the present claims have been amended to specify direct delivery as the route of administration employed. This amendment is, however, made only for the purpose of narrowing the present issues, and is not made with prejudice to presentation of broader claims at a later time.

The remaining questions regarding enablement are therefore whether, based on an understanding of the invention, would one of ordinary skill reasonably expect it to achieve the following: (1) sufficient expression *in situ* of therapeutically effective neurotrophin to produce a therapeutic benefit; and (2) little if any immune response to the vector or gene product.

All of these questions are put to rest by the data submitted herewith, in the Declaration of Dr. Mark Tuszynski submitted in the parent application, a copy of which is submitted herewith. Dr. Tuszynski confirms the results of two sets of experiments using the *in vivo* technique claimed herein in aged animals, as well as art-accepted animal models of Alzheimer's (AD) and Parkinson's Disease (PD) (both non-human primates and rodents were utilized). In these experiments, expression was not only of sufficient volume (> 90% of neurons targeted were transfected) and duration (8+ months, at last testing) to offer a therapeutic benefit to treated animals, a demonstrable improvement in motor function and cognition was confirmed. See, e.g., data presented in Tuszynski Declaration, at ¶ 3, 6, 12, 14-21 and 25-29.

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Expression in these animals has persisted throughout the test period (in excess of 8 months for several animal sets). Although expression may decline over time, the expression which is achieved is sufficient to treat, and possibly even reverse, the cognitive and motor function impairment observed in the test animals. Tuszynski Declaration, at ¶ 3.

Moreover, these results are achieved without detectable inflammation in the brain. Tuszynski Declaration at ¶ 4, 6 and 12. The absence of an adverse immune response to administration of neurotrophin-expressing viral constructs in the brain is not altogether surprising. Immune responses to exogenous material in brain parenchyma (targeted in the invention) are usually muted, in contrast to responses observed in the ventricles or vascular circulation in the brain. See, e.g., Stevenson, *et al.*, *J. Virol.*, 71:145-151 (1997).

The data set forth in the present specification and in Dr. Tuszynski's Declaration demonstrate practice of the invention not only with GDNF, but also with NGF. With respect to the identity of neurotrophins useful in the invention, there is no evidence of record to suggest that any neurotrophin would not be reasonably expected to exert some level of therapeutic benefit if used in the invention. This is certainly true of the families of neurotrophins to which GDNF and NGF belong, the members of which families share substantial structural and functional homologies. For example, the GDNF family of neurotrophins includes neurturin, persephin and artemin, all of which exert similar neurotrophic effects. NGF, NT-3 and NT-4/5 are also related in functionality, and all have been used to stimulate growth of neurons in the nervous system. Hence, one of ordinary skill in the art would reasonably expect the neurotrophins whose use is disclosed and claimed in the application to function in the invention—indeed, claims to the use of all such neurotrophins have been allowed in the parent '174 application, and in the grandparent application now issued as U.S. Patent No. 6,167,888. Nothing in the record compels treating the scope of the present claims with respect to selection of neurotrophins for use in the invention differently.

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Thus, practice of the claimed invention offers the art a reasonable, potentially efficacious and safe method for treating central nervous system disorders. It should be appreciated that the extraordinary achievement represented by the observation of improved function in impaired, treated animals cannot be overestimated, and should not be disregarded. Indeed, these results are in many ways unprecedented.

While some experimental treatments for AD show promise in slowing the progression of the disease, actual improvements in central nervous system function among trial participants remain elusive. For example, in a March 16, 2003 report by Hyman, *et al.* in the on-line edition of *Nature*, researchers reported results from autopsy of a participant in the "Alzheimer's vaccine" trials (targeting development of the beta-amyloid plaques characteristic of the Alzheimer's brain) as follows: "[d]espite the vaccine's apparent reduction of the plaques that typically permeate Alzheimer brain tissue, this study found no evidence that the drug affected beta-amyloid deposits found in the brain blood vessels of this woman as well as in most other individuals with Alzheimer's. The vaccine also failed to reduce certain other key pathological features, including neurofibrillary tangles." Cognitive improvement in this and other vaccine-treated individuals has yet to be demonstrated.

Despite these and similar advances in the treatment of AD, the need for a more effective cure or preventative treatment remains great, even overwhelming. Consider the following statistics:

- Approximately 4 million Americans have Alzheimer's. In a 1993 national survey, 19 million Americans said they had a family member with the disease, and 37 million said they knew someone with Alzheimer's.
- An estimated 14 million Americans will have Alzheimer's disease by the middle of this century (2050) unless a cure or prevention is found.
- One in 10 persons over 65 and nearly half of those over 85 have Alzheimer's disease. A small percentage of people as young as their 30's and 40's get the disease.

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- A person with Alzheimer's will live an average of eight years and as many as 20 years or more from the onset of symptoms.
- U.S. society spends at least \$100 billion a year on Alzheimer's disease. Neither Medicare nor most private health insurance covers the long-term care most patients need.
- Alzheimer's disease is costing American business \$61 billion a year—\$36.5 billion is the cost to business of caregiving (lost productivity from absenteeism of employees who care for family members with Alzheimer's); the rest is the business share of the costs of health and long-term care.
- More than 7 of 10 people with Alzheimer's disease live at home. Almost 75% of the home care is provided by family and friends. The remainder is "paid" care costing an average of \$12,500 per year. Families pay almost all of that out-of-pocket.
- Half of all nursing home residents suffer from Alzheimer's or a related disorder. The average cost for nursing home care is \$42,000 per year but can exceed \$70,000 per year in some areas of the country.
- The average lifetime cost per patient is \$174,000.
- The federal government estimates spending approximately \$598.9 million for Alzheimer research in FY2002.

(Source: American Alzheimer's Association).

While their incidence is not as widespread as AD, other central nervous system diseases, potentially treatable with the invention, are also demanding of resources, and in desperate need of a potential cure. For example, PD is estimated to affect a minimum of 1.5 million Americans, most of which are stricken after age 30. The loss of dopamine production in the brain results in moderately to severely impaired motor function. At present, treatment of PD is strictly directed at controlling symptoms—experts suggest that a potential cure could still be as much as 7-10 years in the offing.

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Despite the resources and high level of skill being applied to development of treatments for central nervous system disorders such as AD and PD, effective treatments have remained elusive. With this context, the evidence indicating that the invention may not only be effective in *slowing* the onset of disease, but may actually *reverse* it to some extent, is nothing less than remarkable, and quite surely satisfies the requirements of Section 112, first paragraph.

Based on the foregoing, Applicants submit that the rejection of the claims under 35 U.S.C. 112, first paragraph as being insufficiently supported by the data provided to establish enablement should be withdrawn.

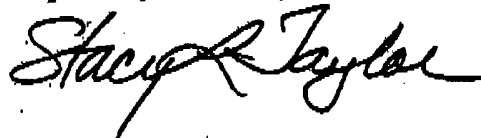
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CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,



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By _____

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